Re: Familial Clustering of Hodgkin Lymphoma and Multiple Sclerosis

We were intrigued by the recent report of Hjalgrim et al. *(1)* that showed familial clustering of multiple sclerosis and young-adult-onset Hodgkin lymphoma in Denmark and that supported Newell's 1970 hypothesis *(2)* of a shared etiology. Their study and another report by Vineis et al. *(3)* indicate a familial association between multiple sclerosis and non-Hodgkin lymphoma.

Given the etiologic importance of these findings, we wanted to evaluate this association further in the larger population of Sweden. Because there is no national multiple sclerosis registry in Sweden, unlike the situation in Denmark, we analyzed hospital discharge diagnoses of multiple sclerosis in relatives of patients with Hodgkin lymphoma and of patients with non-Hodgkin lymphoma compared with relatives of matched control subjects taken from our ongoing studies of familial aggregation of lymphoproliferative tumors. Using our hospital registry approach, we also analyzed our Danish data in the same manner and extended the sample to include relatives of patients with non-Hodgkin lymphoma.

The Swedish Family-Cancer Database has been described previously *(4,5)*. For these analyses, patients with lymphoma, control subjects, and their relatives were linked with the Swedish Hospital Discharge Register from January 1, 1964, through December 31, 2000, which contains individual-based information on discharges from inpatient care. This register has population-based (county-wise) coverage that encompassed more than 90% of the population of Sweden after the mid-1970s and 100% since 1987. We obtained information on all discharges listing multiple sclerosis (International Classification of Disease [ICD], versions 7–10) including dates of discharge. The Danish family data have been described previously *(5)*; patients with lymphoproliferative disease, control subjects, and their relatives were linked with the Danish Hospital Discharge and Outpatient Registers from January 1, 1977, through December 31, 1999, as described above. The population of relatives that we identified is essentially the same as that reported by Hjalgrim et al. *(1)*, which is expected because we used similar methodology to find relatives of patients with Hodgkin lymphoma from the population databases. The numbers of patients, control subjects, and their relatives are shown for each population in Table 1. The outcome was a recorded diagnosis of multiple sclerosis. We tested for increased risk of multiple sclerosis in relatives by using a marginal survival model with a robust variance estimate to account for familial dependencies *(6)*. We use relative risk (RR) to denote the hazard ratio. Risk was also computed by type of relative and by age of Hodgkin lymphoma/non-Hodgkin lymphoma onset in the proband.

Similar to the report of Hjalgrim et al. *(1)*, we found an increased risk of multiple sclerosis (RR = 1.98, 95% CI = 1.15 to 3.42; $P = .01$) when analyzing all first-degree relatives of Danish patients with Hodgkin lymphoma; the highest risk was recorded in siblings (RR = 2.91, 95% CI =1.01 to 8.37; $P = .05$) and in relatives of a proband with young-adult-onset Hodgkin lymphoma (RR = 2.23, 95% CI = 1.23 to 4.05; $P = .01$) (Table 1). In contrast, only a very modest and statistically non-significant increase was observed in the larger Swedish population of first-degree relatives of Hodgkin lymphoma probands. The highest risk was in offspring, and there was no increased risk among relatives of young adult probands. The combined sample shows a modest but statistically significantly elevated risk (RR = 1.51, 95% CI =1.07 to 2.15; $P = .02$).

In relatives of patients with non-Hodgkin lymphoma, a statistically significantly increased risk of multiple sclerosis was found among first-degree relatives of Danish patients (RR = 1.58, 95% CI = 1.08 to 2.32; $P = .02$) (Table 1), which was more prominent among relatives of young-adult-onset probands (RR = 2.06, 95% CI = 1.12 to 3.78; $P = .02$). In Swedish relatives of patients with non-Hodgkin lymphoma, the combined data showed a statistically significant 30% increase risk of multiple sclerosis, with the highest risk in relatives of young-adult-onset probands.

In summary, using a larger Swedish data set to evaluate the reported increased risk of multiple sclerosis in relatives of patients with Hodgkin lymphoma *(1)*, we found a substantially more modest, 29% statistically non-significant increased risk of multiple sclerosis among

Table 1. Relative risk (RR and 95% confidence interval [CI]) for development of multiple sclerosis (MS) in families affected with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL)

	HL			NHL		
	Sweden	Denmark	Combined*	Sweden	Denmark	Combined*
No. case patients†	5047 (7)	2427 (3)	7474 (10)	19651 (16)	6290 (11)	25941 (27)
No. control subjects†	10078 (23)	8495 (15)	18573 (38)	38981 (79)	19572 (50)	58553 (129)
Personal RR of MS after HL/NHL (95% CI)	— ‡	— ‡	0.82 (0.34 to 2.01)	— ‡	— ‡	0.62 (0.31 to 1.26)
No. case relatives†	15799 (35)	7284 (21)	23083 (56)	54627 (115)	15081 (40)	69708 (155)
No. control relatives†	32117 (53)	27900 (39)	60017 (92)	108969 (189)	51174 (80)	160143 (269)
Familial RR (95% CI)						
All relatives§	1.29 (0.83 to 2.00)	1.98 (1.15 to 3.42)	1.51 (1.07 to 2.15)	1.21 (0.96 to 1.53)	1.58 (1.08 to 2.32)	1.30 (1.06 to 1.59)
Age of proband						
15–44 y	1.15 (0.60 to 2.20)	2.23 (1.23 to 4.05)	1.62 (1.02 to 2.56)	1.69 (0.85 to 3.36)	2.06 (1.12 to 3.78)	1.77 (1.16 to 2.72)
≥45 y	1.40 (0.75 to 2.59)	0.86 (0.17 to 4.20)	1.30 (0.74 to 2.30)	1.19 (0.92 to 1.52)	1.23 (0.73 to 2.10)	1.17 (0.93 to 1.48)
Defined relative						
Offspring	1.74 (0.96 to 3.18)	2.05 (0.83 to 5.06)	1.82 (1.11 to 3.01)	1.19 (0.91 to 1.56)	1.39 (0.86 to 2.26)	1.24 (0.98 to 1.56)
Parents	0.87 (0.32 to 2.33)	1.45 (0.57 to 2.69)	1.12 (0.55 to 2.27)	0.92 (0.43 to 1.98)	2.02 (0.94 to 4.34)	1.32 (0.76 to 2.31)
Siblings	1.04 (0.44 to 2.46)	2.91 (1.01 to 8.37)	1.50 (0.75 to 3.00)	1.65 (0.90 to 3.02)	1.85 (0.56 to 6.12)	1.68 (0.98 to 2.90)

*Combined analyses were corrected for country.

†Numbers of individuals affected with multiple sclerosis are shown in parentheses.

‡Data are not given because of small numbers.

§If follow-up time in relatives was restricted to after the proband's diagnosis, results were virtually the same; all analyses were corrected for sex.

first-degree relatives of Swedish patients with Hodgkin lymphoma and a modest 51% increased risk in the combined sample. We also found a similarly modest, statistically non-significant increased risk of multiple sclerosis among Swedish relatives of patients with non-Hodgkin lymphoma, although the 30% increased risk in the combined sample was statistically significant (P = .02). A potential limitation of our study is that the multiple sclerosis outcomes were from the hospital discharge registries and were not validated. However, because multiple sclerosis was assessed among relatives of matched control subjects with the same hospital registries, the relative risks should not be biased. This is supported by our finding of a similar relative risk of multiple sclerosis among relatives of Hodgkin lymphoma cases as found by Hjalgrim et al. *(1)*. Originally, an association between multiple sclerosis and Hodgkin lymphoma was suggested because of some ecological correlation *(2)*, but this was disputed by others *(7)*. In their report, Hjalgrim et al. *(1)* suggested that the familial clustering of multiple sclerosis and Hodgkin lymphoma could represent common etiologic factors. Although the more modest relationship observed in Sweden and the similarly modest familial clustering of multiple sclerosis and non-Hodgkin lymphoma do not negate the interpretation, the unknown shared etiologic factor(s) in multiple sclerosis and Hodgkin lymphoma/non-Hodgkin lymphoma is likely of only minor importance.

Ola Landgren
Kimberly F. Kerstann
Gloria Gridley
Lene Mellemkjaer
Kari Hemminki
Martha S. Linet
Lynn R. Goldin

References

(1) Hjalgrim H, Rasmussen S, Rostgaard K, Nielsen NM, Koch-Henriksen N, Munksgaard L, et al. Familial clustering of Hodgkin lymphoma and multiple sclerosis. J Natl Cancer Inst 2004;96:780–4.

(2) Newell GR. Etiology of multiple sclerosis and Hodgkin's disease. Am J Epidemiol 1970;91:119–22.

(3) Vineis P, Crosignani P, Vigano C, Fontana A, Masala G, Stagnaro E, et al. Lymphomas and multiple sclerosis in a multicenter case-control study. Epidemiology 2001;12:134–5.

(4) Hemminki K, Li X, Plna K, Granstrom C, Vaittinen P. The nation-wide Swedish family-cancer database—updated structure and familial rates. Acta Oncol 2001;40:772–7.

(5) Goldin LR, Pfeiffer RM, Gridley G, Gail MH, Li X, Mellemkjaer L, et al. Familial aggregation of Hodgkin lymphoma and related tumors. Cancer 2004;100:1902–8.

(6) Pfeiffer RM, Goldin LR, Chatterjee N, Daugherty S, Hemminki K, Pee D, et al. Methods for testing familial aggregation of diseases in population-based samples: application to Hodgkin lymphoma in Swedish registry data. Ann Hum Genet 2004;68:498–508.

(7) Kurtzke JF, Hamtoft H. Multiple sclerosis and Hodgkin's disease in Denmark. Acta Neurol Scand 1976;53:358–75.

Notes

Affiliations of authors: Genetic Epidemiology Branch (OL, KFK, LRG), Radiation Epidemiology Branch (MSL), and Biostatistics Branch (GG), Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; Department of Biosciences at Novum, Karolinska Institute, Stockholm, Sweden (KH); Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark (LM); Division of Molecular Genetic Epidemiology, German Cancer Research Center, Heidelberg, Germany (KH).

Correspondence to: Ola Landgren, MD, PhD, Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., Bethesda, MD (e-mail: landgreo@mail.nih.gov).

DOI: 10.1093/jnci/dji092

RESPONSE

In a series of analyses, we recently observed an increased risk of multiple sclerosis (relative risk [RR] = 2.25, 95% confidence interval [CI] = 1.24 to 4.06) in first-degree relatives of patients with Hodgkin lymphoma and, independently hereof, an analogously increased occurrence of young-adult Hodgkin lymphoma (RR = 1.93, 95% CI = 1.01 to 3.71) in first-degree relatives of patients diagnosed with multiple sclerosis in a Danish register–based investigation *(1)*.

The observed clustering of these two conditions is interesting because it may reflect that they share common risk factors and because the clustering may form the basis for new etiological

hypotheses. In recognition of the absence of similar reports in the literature, however, we encouraged other researchers to verify our observations.

Landgren et al. have taken up this challenge and (re)analyzed Danish and Swedish cancer and hospital discharge register data. Using more elaborate statistical techniques combining the time periods before and after the exposure-defining lymphoma diagnosis, they observe a 1.98-fold increased risk for multiple sclerosis in first-degree relatives of Danish Hodgkin lymphoma patients and a, more modest, 1.29-fold increased risk for multiple sclerosis in first-degree relatives of Swedish patients with Hodgkin lymphoma. Thus, these new Danish-Swedish analyses suggest a relative risk of 1.51 (95% CI = 1.07 to 2.15) for multiple sclerosis in the combined group of all first-degree relatives of patients with Hodgkin lymphoma.

Although different statistical approaches make direct comparison of risk estimates difficult, we agree with the authors that there is good agreement between our previous results using the Danish Multiple Sclerosis Register and the current series of analyses using Danish hospital discharge data. In our view, however, this consistency does not necessarily imply that the results of analyses of Swedish data should be interpreted uncritically. The possible implications of the various gaps in the Swedish Family Register and parental information missing for 50% of offspring dead before 1991 *(2)* are unclear to us, and we also disagree that diagnostic misclassification in the hospital discharge data, the extent of which may well differ between Denmark and Sweden, can automatically be presumed unimportant.

With these precautions, therefore, it would seem that the most important finding of the current investigation is the confirmation of the previously observed familial clustering of Hodgkin lymphoma and multiple sclerosis *(1)*.

Henrik Hjalgrim
Klaus Rostgaard
Nete Munk Nielsen
Nils Koch-Henriksen
Lars Munksgaard
Hans H. Storm
Mads Melbye

References

(1) Hjalgrim H, Rasmussen S, Rostgaard K, Nielsen NM, Koch-Henriksen N, Munksgaard L, et al. Familial clustering of Hodgkin lymphoma and multiple sclerosis. J Natl Cancer Inst 2004;96:780–4.

(2) Goldin LR, Pfeiffer RM, Gridley G, et al. Familial aggregation of Hodgkin lymphoma and related tumors. Cancer 2004;100:1902–8.

Notes

Affiliations of authors: Department of Epidemiological Research, Statens Serum Institut, Copenhagen, Denmark (HH, KR, NMN, LM, MM); National Institute of Public Health, Copenhagen, Denmark (NK-H); Department of Neurology, Aarhus University Hospital in Aalborg, Aalborg, Denmark (NK-H); Department of Cancer Prevention and Documentation, Danish Cancer Society, Copenhagen, Denmark (HHS).

Correspondence to: Henrik Hjalgrim, MD, Department of Epidemiological Research, Statens Serum Institut, Copenhagen, Denmark (e-mail: hhj@ssi.dk).

DOI: 10.1093/jnci/dji093